Maple Syrup Urine Disease (MSUD)

Biochemistry 5614 Service-Learning Initiative Autumn 2020

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Occurrence frequency

- United States population

  - Estimated frequency of approximately 1 in 220,000 live births

- The Mennonite population (United States)

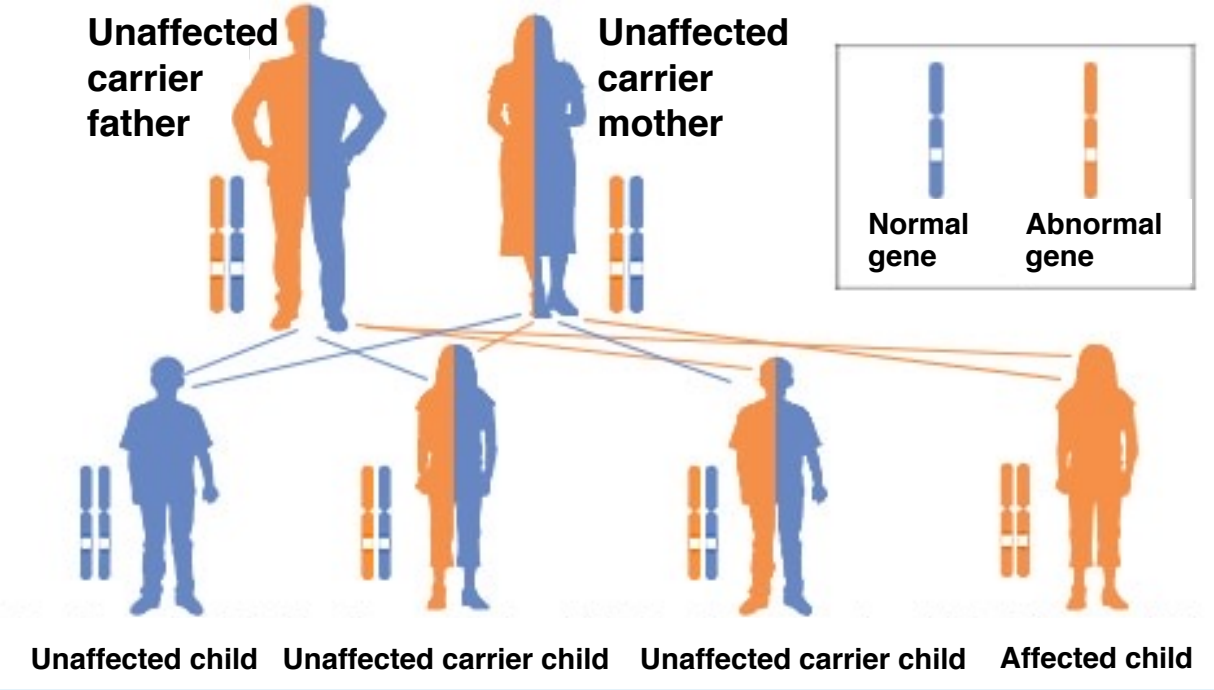
  - Estimated frequency of approximately 1 in 380 live births

  (The much higher frequency among the Mennonites is due to the founder effect, i.e., when inbreeding in isolated groups results in a small gene pool with persistence of genes/mutation)

- A child may have increased risk of MSUD due to both parents being carriers of a spontaneous/random mutation, of Mennonite lineage, or both

Genetics

- Autosomal recessive disorder (i.e., two mutant copies needed to manifest disease)
- The mutation could be in one of three genes that code for the branched chain α-keto-acid dehydrogenase complex (BCKD), which breaks down three branched chain amino acids



Digital image retrieved Apr 7, 2021
from https://www.mayoclinic.org/tests-procedures/genetic-testing/multimedia/genetic-disorders/sls-20076216?s=4

Genetics overview video

https://youtu.be/Nv6qUsKYodA

Major food groups*

Carbohydrates

Fats

Proteins

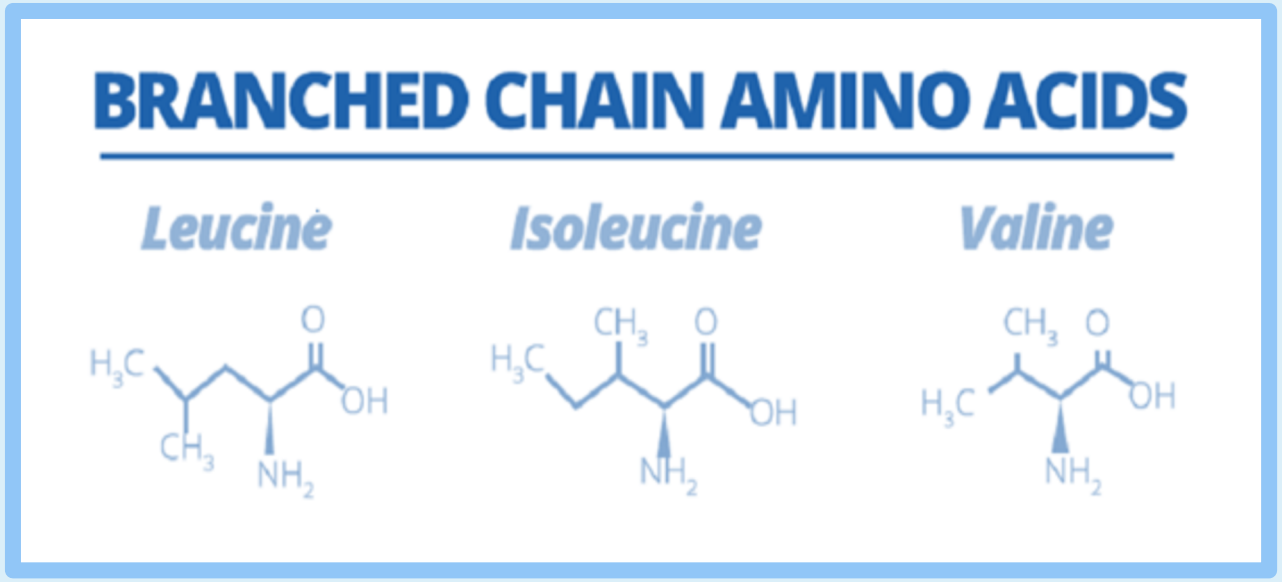
MSUD associated with a defect in protein utilization

* Each exemplar shown above was chosen because of its representative value to the respective group but note that the depicted item is not entirely devoid of the two other food groups

Nature of the problem in MSUD

Amino acids are the building blocks of proteins

In MSUD, defective BCKD enzyme cannot break down these three essential* amino acids



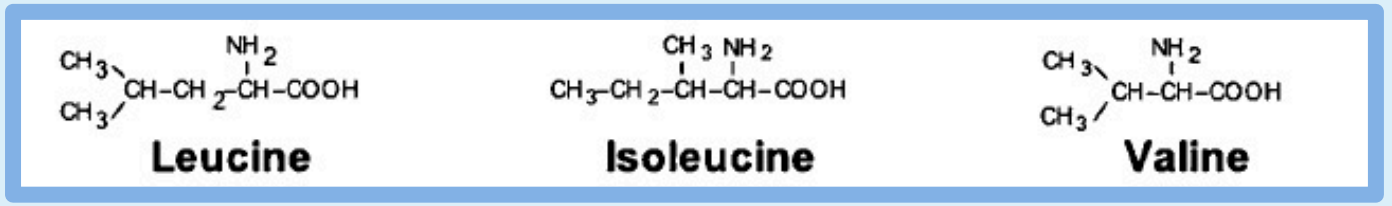
Digital image retrieved Nov 7, 2020 from
https://killcliff.com/blogs/hpc/do-you-need-bcaas

* Essential refers to those amino acids that the body cannot make and must therefore be obtained from the diet

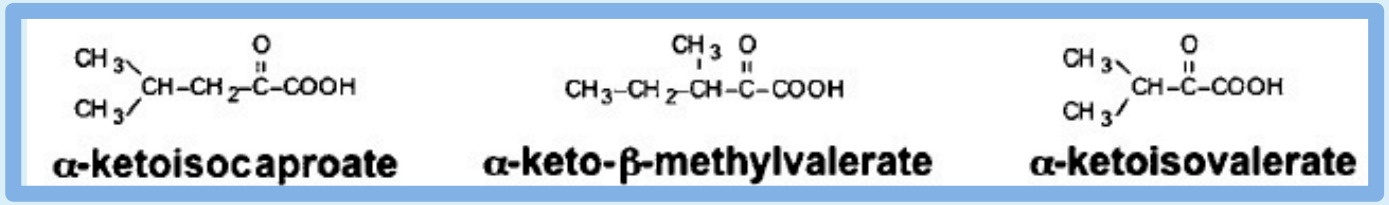
Biochemical features

- Defective BCKD enzyme – variants of MSUD have varying severity of deficits in activity
- Build-up of branched chain amino acids and α-keto acids (reflected in high levels in blood and urine)
- Stools, urine, sweat, and earwax that smells of maple syrup, the odor associated with α-keto acids

Branched Chain Amino Acids (BCAAs)



α-keto acids



Digital image retrieved Nov 7, 2020 from
https://nickrauh.wordpress.com/2014/03/20/biochemistry/

Symptoms

- Symptoms can appear starting about 3 days after birth as the toxic metabolites accumulate; symptoms include:
  - **Bodily fluids smell of maple syrup**
  - Poor feeding, vomiting, loss of appetite, irritability
  - Tiredness and weakness
  - Poor muscle tone (”floppy”) or stiffness of muscles
  - Abnormal muscle movements
  - Developmental delay
  - Seizures and convulsions leading to respiratory failure/coma

- Severity of symptoms may be dependent upon which clinical variant of MSUD an individual has

Diagnosis

- Birth
  - Newborn screening
  - May result in a false negative due to lack of adequate time for measurable accumulation of toxic metabolites
- Post birth/toddler
  - Analysis of plasma, urine, and white blood cells, symptom assessment
  - Amino acid and BCKD enzyme testing to check for elevated levels

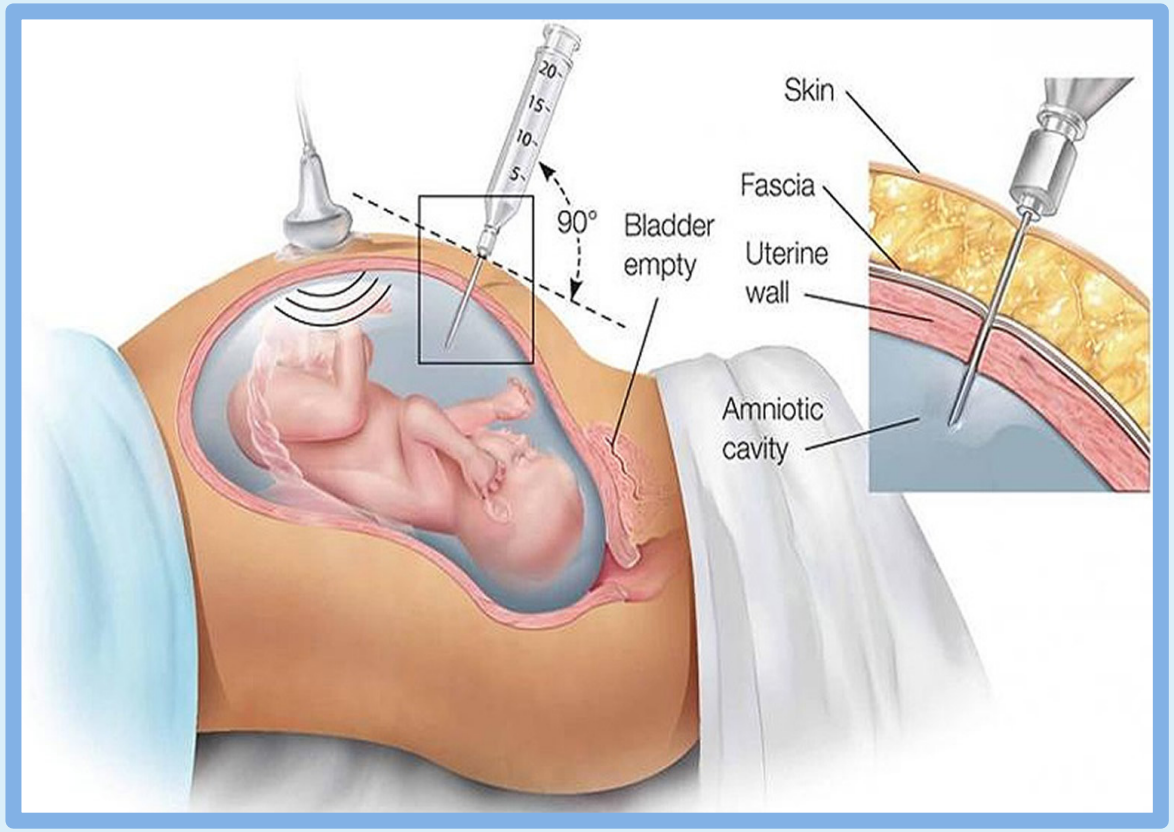
Newborn screening

Digital image retrieved Nov 07, 2020 from https://www.af.mil/News/Photos/igphoto/2000419731/

Prenatal diagnosis

If a fetus is predisposed to MSUD (based on either family history or previously affected child), two prenatal diagnosis methods can be used for testing of BCKD enzyme activity:

- **Chorionic villus sampling:** performed at 11-14 weeks; biopsy of cells from mother's placenta for testing; low risk of amniotic leakage or of infection
- **Amniocentesis:** performed at 15-20 weeks; amniotic fluid is removed and tested; some risk of amniotic leakage and infection

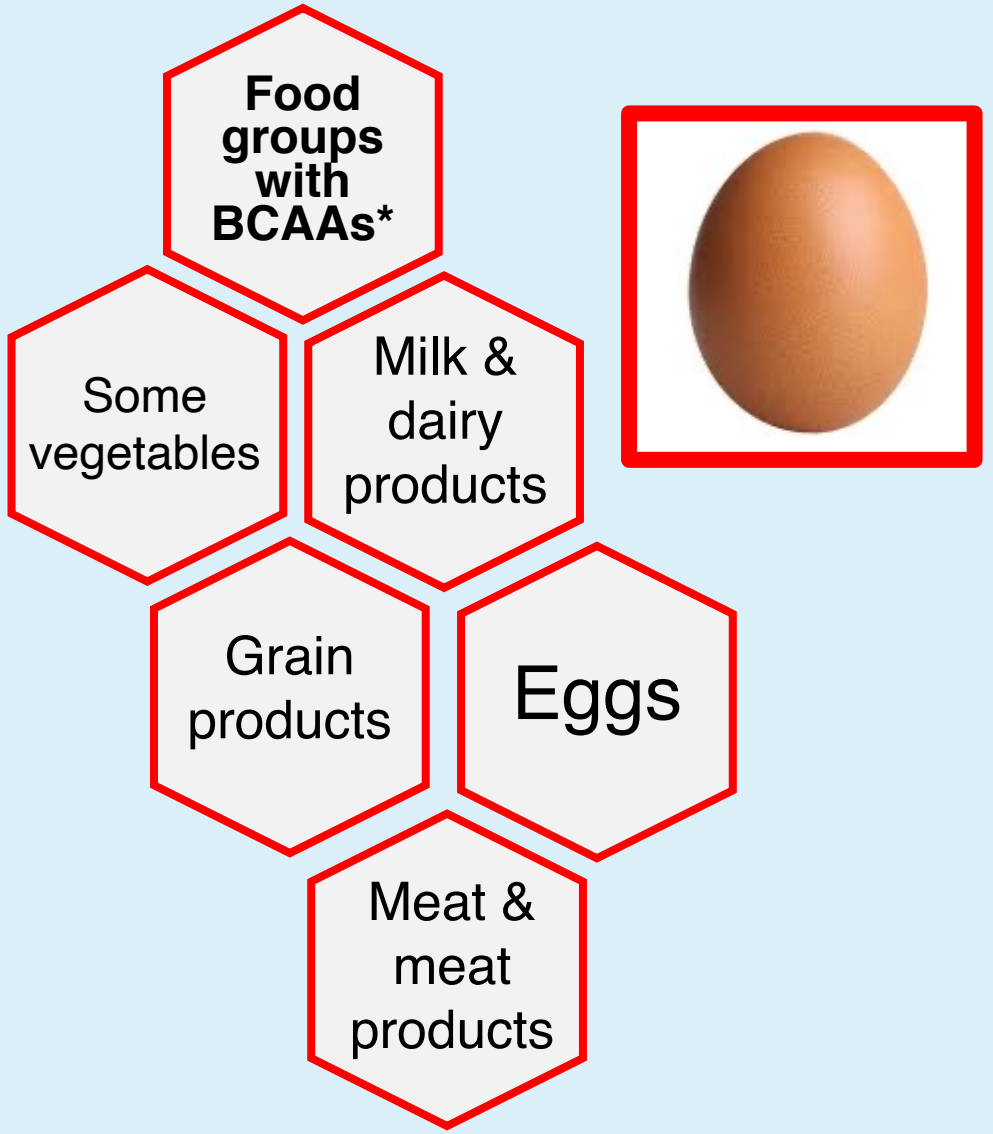


Amniocentesis

Digital image retrieved Nov 7, 2020 from https://www.mayoclinic.org/tests-procedures/amniocentesis/about/pac-20392914

Therapy

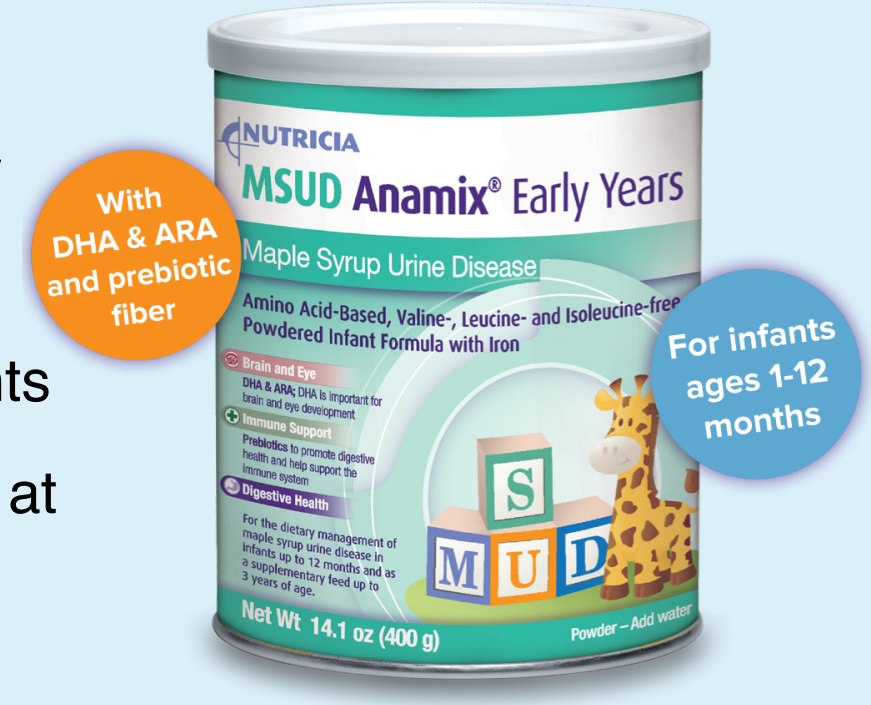
- Strict high-calorie diet to prevent breakdown of body's energy stores and weight loss
- Limit intake of leucine, isoleucine, and valine (present in all proteins); intake is limited for infants by specialized formulas
  - Underestimating intake may result in development of symptoms
- Frequently monitor levels of BCAAs in the blood (twice a week for infants and weekly for older children/adults)
- Liver transplant to restore functional enzyme; albeit a possibility, this approach has its own risks, and it will not prevent the defective MSUD gene to be passed onto children



* An individual with MSUD must limit dietary intake of these food types to avoid a metabolic crisis

Prognosis

- Maple Syrup Urine Disease is managed through strict diet
  - BCAA-free formula for infants provides necessary dietary sustenance without harmful BCAAs
  - BCAAs are supplemented into the diet in very low amounts
  - However, even with strict diet control, an individual is still at high risk for metabolic attack
- An affected individual can grow into adulthood with normal development
- Symptoms will vary in intensity based on the relative activity of the enzyme in affected individuals



MSUD Formula

Digital image retrieved Nov 07, 2020 from https://www.msudsupport.org/newsletters/116-volume-33-2/619-introducing-new-infant-formula-for-msud

Available support

MSUD Family Support Group

- Access to current, relevant MSUD research
- Network of MSUD-specific dieticians, physicians, and facilities

Organic Acidemia Association

- Information on diagnosis procedures
- Facebook support group, conferences, and research fundraising

National Organization for Rare Disorders

- Patient and family advocacy
- Information for financial assistance and research opportunities

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Contributors

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Zechariah Shearer	Genetics
Josh Gilger	Symptoms
Claudia Studebaker	Diagnosis